A Study On Minimal Hepatic Encephalopathy

Dissertation submitted in partial fulfillment of the requirements for the degree of

D.M. (MEDICAL GASTROENTEROLOGY)

Branch – IV

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI

AUGUST 2009

Certificate

This is to certify that Dr**. J. Antony Joe** has been a post graduate D.M (Gastroenterology) student during 2006 – 2009 in the Department of Medical Gastroenterology, Madras Medical College and Government General Hospital, Chennai.

This dissertation titled **" A STUDY ON MINIMAL HEPATIC ENCEPHALOPATHY "** is a bonafide work done by him during the study period is being submitted to the Tamilnadu Dr. M.G.R. Medical University in partial fulfillment of D.M Branch IV Medical Gastroenterology Examination.

Prof. A. Mohammed Ali,
Head of the Department,
Dept of Medical Gastroenterology,
Madras Medical College,
Government General Hospital,
Chennai-600003.

Dean,
Madras Medical College,
Government General Hospital,
Chennai-600003.

Declaration

I solemnly declare that this dissertation **" A Study On Minimal Hepatic Encephalopathy "** was prepared by me in the Department of Medical Gastroenterology, Madras Medical College and Government General Hospital, Chennai under the guidance and supervision of professor and HOD Department of Medical Gastroenterology, Madras medical College and Government General Hospital, Chennai between January 2008 and December 2008.

This dissertation is submitted to the Tamilnadu Dr. M.G.R Medical University, Chennai in partial fulfillment of the university requirements for the award of degree of DM Medical Gastroenterology.

Place : Chennai

Date : 2.06.2009

ACKNOWLEDGEMENT

I thank the Dean, Madras Medical College for permitting me to carry out this study and also for providing necessary facilities.

I thank Prof. Mohammed Ali, D.M., Head, Department of Medical Gastroenterology for his valuable guidance, suggestions and constant encouragement.

My thanks are due to Prof. P. Padmanabhan, D.M., Additional Professor, Department of Medical Gastroenterology for his counseling and constructive suggestions.

I sincerely thank Prof. V. Natarajan, D.M., Professor, Department of Neurology for his support and help in carrying out the study.

I express my gratitude to Dr. P. Ganesh, Dr. K. Premkumar and Dr. Caroline Selvi for their support, interest and enthusiasm in completion of this study.

I thank my colleagues, Dr. Mahadevan, Dr. B.J. Gokul, Dr. Karthikeyan, Dr. Vinoth and Dr. Kani Shaik Mohammed for their help and assistance in successfully completing this study.

I thank my family members who stood by me in successfully completing this study.

I thank all the patients who cooperated with me in carrying out this study, in spite of their illness. This work would be complete and successful, if it had contributed, even in the smallest possible way, to alleviate their suffering.

CONTENTS

Chapter	Title	Page No
1.	Introduction	1
2.	Aim of the Study	4
3.	Review of Literature	5
4.	Materials & Methods	42
5.	Results	48
6.	Discussion	52
7.	Conclusion	54
8.	Bibliography	55
9.	Appendix	64

Introduction

Minimal hepatic encephalopathy (MHE) is the earliest stage of hepatic encephalopathy and is associated with changes in cognitive functions, in electrophysiological parameters and in cerebral neurochemical/ neurotransmitter homeostasis. MHE can be observed in patients with cirrhosis who have no clinical evidence of hepatic encephalopathy.

Prevalence is estimated to be about 30% - 60% in cirrhotics without overt clinical signs of hepatic encephalopathy [1-7] . Probability of clinical hepatic encephalopathy after follow up of 3years was estimated to be 50% in patients with MHE compared to 8% in cirrhotics without MHE, whether this course of events is affected by early treatment needs to be studied.

MHE often manifested with sleep disturbances or subtle behavioral changes that are more apparent to the patient's family than to the clinician. The behavioral changes are due predominantly to subtle impairment of cognitive function resulting from bilateral dysfunction of forebrain and parieto-occipital regions, because verbal abilities are usually preserved in this stage of hepatic encephalopathy. Cerebral dysfunction is not detectable by the routine clinical examination but only by neuropsychological or neurophysiological measures.

Patients with MHE perform worse than healthy controls especially in tests of psychomotor speed, visual perception and attention. Some of these patients also show a

pathologic slowing of the electroencephalogram (EEG) and prolonged latencies of exogenous (visual evoked potentials (VEP), somatosensory evoked potentials (SSEP) and brainstem auditory evoked potentials (BAEP) and endogenous evoked potentials (P300).

Table 1. Prevalence of MHE

Author (year)	N	Modality of diagnosis	Prevalence (%)
Yen et al (1990)	97	NCT	60
Groenweg et al (2000)	179	BAEP Psychometry	27
Das et al (2001)	165	EEG Psychometry	63
Saxena et al (2001)	101	P300 auditory evoked potential	21
Liu et al (2004)	97	NCT	60
Sharma et al (2007)	156	BAEP P300 auditory evoked potential	53
Prasad et al (2007)	90	Psychometry Psychometry	68

Although undetectable on clinical grounds MHE is undoubtedly of clinical significance for the patients. It has been shown to interfere with the patient's ability to drive a car, their earning capacity and their quality of life. Therefore experts in the field

discourage the use of the terms subclinical encephalopathy or latent hepatic encephalopathy.

A consensus has emerged that patients with MHE should be treated. Only limited numbers of studies are available to analyze the importance of encephalopathy. Hence psychometric and neurophysiological tests to diagnose minimal hepatic encephalopathy. We have undertaken this study to find out the prevalence of minimal hepatic encephalopathy in patients with cirrhosis of different etiology.

AIM OF THE STUDY

To find out the prevalence of Minimal Hepatic Encephalopathy in cirrhotic patients with the help of Number connection test (NCT), Electroencephalogram (EEG) And Brainstem auditory evoked potential (BAEP).

REVIEW OF LITERATURE

MHE has generated a lot of interest in recent years. There is increasing evidence to show that MHE is an important disorder that could seriously impair daily living and health related quality of life (HRQOL) in patients with cirrhosis.[4, 5] Treatment with lactulose is of benefit as it improves both cognitive functions and HRQOL.[8] Diagnosis of MHE requires a high index of suspicion.

MHE is defined as the condition in which patients with liver cirrhosis show several quantifiable neuropsychological defects together with a normal neurological examination. The pathogenesis of MHE is not yet clear.

Treatment with lactulose is of benefit as it improves both cognitive functions and HRQOL. Treatment with synbiotics or fermentable fiber is an alternative to lactulose for management of MHE in patients with cirrhosis. Cirrhotic patients may be routinely screened for the presence and treatment of MHE.

Subcortical alterations in the basal ganglia has been suggested as a possible anatomical site responsible for the subclinical changes of this entity. The selective reduction in glucose consumption in the area of the cyngulate gyrus, a nucleus involved in the attention process, coupled with focal alterations of cerebral perfusion support this hypothesis. On the other hand, the relation of subclinical changes to protein metabolism and plasma amino acid imbalance, the reduction in cerebral blood flow and the improved response of neuropsychological tests after therapeutic

manipulations which are applied in clinically overt HE, suggest the impact of the liver disease on brain function.

The incidence of MHE is estimated to vary from 30% to 84% in apparently healthy, non-encephalopathic cirrhotic patients, depending on the diagnostic criteria used.[12-16] This large variation reflects the variability and the large number of tests used and, on the other hand, is related to the composition of the tested population in each study, especially to the severity and the etiology of their cirrhosis. Although the diagnosis of symptomatic HE is a diagnosis of exclusion, based mainly on a careful global and neuropsychiatric examination, MHE is not a clinically evident entity and thus, for their detection, requires specific neuropsychological and neurophysiological examination.

Historical aspects

In 1957 Passons-Smith et al. identified the presence of definite Electroencephalographic (EEG) abnormalities in 43% of cirrhotic patients without overt Hepatic Encephalopathy. The authors did not realize the importance of their findings, which in effect defined the existence of a latent or preclinical stage of hepatic encephalopathy (HE).

In 1970, Zeagen et al. observed that 62% of a cohort of patients who had undergone Porto-systemic shunt surgery showed impaired performance of the Trail-Making Tests A and B even though their mental function was apparently normal. In

1978, Rikkers et al evaluated a group of cirrhotic patients who had undergone Porto-systemic shunt surgery but whose mental state was deemed to be unimpaired; they observed EEG abnormalities in 33% and impaired psychometric performance in 60%. The authors coined the term subclinical Hepatic Encephalopathy.

Nomenclature and Grading of Hepatic encephalopathy

Working Party at the 11th World Congress of Gastroenterology, Vienna under the Organisation Mondiale de Gastroentrologie proposed multiaxial definition of HE that defines both the type of hepatic abnormality and the duration/characteristics of neurological manifestations in chronic liver disease HE has been considered a continuous dimension that could be measured

with one index to summarize several neurological domains, such as, cognition, emotion, behavior, or biologic rhythms. Minimal hepatic encephalopathy (MHE) would represent a portion of this dimension, would be the mildest form of HE, and would be diagnosed on the basis

of a cut-off score.

Table : 2 West Haven Staging of Hepatic Encephalopathy

Stage	Criteria
0	No abnormality
1	Trivial lack of awareness; euphoria or anxiety; shortened attention span; impaired performance of addition
2	Lethargy or apathy; disorientation for time and place; subtle personality change; inappropriate behavior; impaired performance of subtraction
3	Somnolence to semi-stupor but responsive to stimuli; confusion; gross disorientation
4	Coma, mental state not testable

Recently, use of the term subclinical HE has been criticized mainly because such a term might trivialize the condition because its presence has a detrimental effect on health related quality of life, may predict overt HE and may carry poor prognosis. Present consensus favors the term that was coined by Schomerus and Hamster. This term also signify that MHE represents the mildest form of HE and represent one end of the continuous dimension.

Figure 1: Hepatic encephalopathy: A continuous dimension

MHE is not a clinically evident entity and thus, for their detection, requires specific neuropsychological and neurophysiological examination.

Precipitating factors for Hepatic Encephalopathy

Evaluation should include work up to look for the precipitating factors and strict attention must be paid in treating following precipitating factors:

1. Infection: spontaneous bacterial peritonitis, urinary or respiratory tract infections; appropriate cultures are required.
2. Nitrogen overload: gastrointestinal bleed, uremia, constipation and or excessive consumption of proteins, etc; placement of nasogastric tube and stool analysis is required to exclude gastrointestinal bleed.

3. Metabolic: hypokalemia, alkalosis, hyponatremia, renal failure, dehydration: prompt identification followed by correction of these metabolic factors are mandatory.
4. Additional hepatic injury: portal vein thrombosis or superimposed hepatitis (viral, alcoholic or drug induced).
5. Drugs: opiates, benzodiazepines, sedatives, diuretics: urinary screening for narcotics or benzodiazepines may be required at times.

Pathogenesis of Hepatic Encephalopathy

HE is a form of gliopathy caused due to swelling of Alzheimer type II astrocytes, the only cerebral cell capable of metabolizing ammonia. Ammonia and other intestinal neurotoxins,[39] manganese and the benzodiazepine-GABA system are the main substances implicated in the development of HE. Neurotransmission changes induced by these compounds play a major role
in the development of the neurologic disturbances presented in these patients.

Ammonia remains the first key gut-derived neurotoxin implicated in the pathogenesis of HE; the highest concentrations are found in the portal vein. Ammonia, derived from colonic bacteria as well as from the deamination of glutamine in the small bowel, is absorbed by passive diffusion and undergoes a high first-pass extraction by the liver. In liver failure, hepatic urea synthesis declines and this, along with portal-systemic shunting, leads to increased arterial blood ammonia concentrations. Ammonia is primarily responsible for encephalopathy that has been substantiated by recent studies. [41,46] A study has shown that arterical NH3 levels >
200 µg/dL in patients with stage III-IV encephalopathy was an accurate predictor of herniation in patients with acute liver failure.

[43] The blood-brain barrier permeability to ammonia is increased in patients with HE. Ammonia is detoxified in astrocytes by glutamine synthetase leading to formation of glutamine, the accumulation of which is the major cause of astrocyte swelling.

[44] Ammonia also effects the neurons by inducing neurosteroid production leading to a positive modulatory effect on the γ-aminobutyric and A (GABA-A) receptors leading to upregulation of peripheral benzodiazipine receptors thus causing a functional imbalance between the excitatory and inhibitory receptor systems. The upregulation of GABA-A receptors in HE is a form of denervation supersensitivity and is associated with decreased GABA at neuronal level rather than an increased GABA levels in blood and brain.

Indeed, animal studies have shown that mild encephalopathy is characterized by a 45%-50% increase in the number of GABA receptors without change in the affinity constants. [45,46] These findings have recently been confirmed in humans where increased

central type benzodiazepine receptors and decreased cortical GABA levels were demonstrated in patients with recurrent HE. [47] Thus, these changes explain the supersensitivity to benzodiazepines in patients with acute and chronic liver disease. Hence ammonia induces HE by multiple mechanisms and is the main pathogenetic factor.

Natural benzodiazepines (NBZDs) such as diazepam and nordiazepam are naturally present in several plants, vegetables, and animal species and in humans. [48] Microorganisms in gut flora like *Acinatobacter lwoffi* can also produce NBZDs. NBZDs are found in trace amount in normal subjects but may increase several fold in patients with cirrhosis. [48] A significant but 7 weak correlation between NBZDs and the degree of HE has been demonstrated by Basile and coworkers. [49] A recent study showed a 40% reduction in NBZDs levels after reduction in bacterial flora with riflaximin. [50] Thus NBZD might be contributing to the pathogenesis of HE.

Neurophysiologic assessment of MHE

MHE is characterized by psychomotor slowing, disturbances of motor speed and accuracy and deficits in attention, visual perception and visual orientation and visuoconstructive abilities. Various studies have been performed to evaluate psychometric tests together with or without neurophysiologic measures such as EEG and evoked potentials for their sensitivity and reliability in the diagnosis of MHE. Diagnostic approach to the assessment of MHE is not uniform and no gold standard exists.

Most of the studies recommend uniformly the administration of the same few tests such as, the NCT A & B, the digit symbol test or the block design test, a line training test and a serial dotting test.

NCT-B provided a higher sensitivity and specificity as the various neurophysiologic measures used. (EEG, VEP, P300)

Since the beginning of the 1970s, more than sixty different diagnostic tests and eight test batteries have been proposed and used for the diagnosis of MHE, which can be classified in four major groups.

1. PSYCHOMETRIC OR NEUROPSYCHOLOGICAL TESTS

Zeegen et al in the early 1970s, first demonstrated an abnormal score in approximately one third of 39 apparently healthy cirrhotic patients previously operated for portal decompression using the Reitan trail making tests.

Thereafter, neuropsychologists have designed and used more than 25 psychometric tests for the detection of MHE with most common neuropsychological finding an impairment of motor speed and accuracy, accompanied with deficits in visual perception, visuospatial orientation, visual construction, concentration, attention and memory while the verbal ability is preserved. From all these psychometric examinations and according to the grade of their diagnostic accuracy, four can be considered as the most sensitive:

I) the Number Connection Test

(NCT), available in two versions, part A and part B

ii) The Digit. Symbol Test (DST)

iii) the Block Design Test

(BlDes) and

iv) the Reaction Time to Light or Sound

Test (RT).

Although psychometric tests are characterized by high sensitivity and simplicity in performance, their interpretation is not as easy as suggested because a number of factors can influence the overall score. A proposed correction using the adequate age normalized values is not the solution to the problem, because the final result is also influenced by the grade of cirrhosis, the educational level and the cultural background of the examined population, as well as subject to the effect of repeated learning.

A history of alcohol abuse also induces a minor influence in MHE diagnosis, as reported by several investigators. Thus to abolish this effect, the use of different test variants of equal difficulty has been suggested. Taking into account that a different domain of cognitive functioning is measured by each psychometric test (NCT measures cognitive motor abilities, SDT motor speed and accuracy etc.) several authors have been proposed their use in combination (test batteries). The proposed comparison, between different neuropsychological domains can be also a useful diagnostic approach for this form of HE. But, despite the efforts and the progress, there is not yet a gold standard for the neuropsychological assessment of MHE. Although psychometric tests are characterized by high sensitivity, their specificity and their positive predictive value are low.

The newly developed computerized psychometric tests, Posner test, Sternberg Paradigm appear to be very promising tools, but experience is still limited. The statement of the Consensus conference of the 11th World Congress of Gastroenterology proposed that at least two of the following psychometric examinations should be used:
NCT-A, NCT-B, BIDes, DST.

A standardized test batteries that include the NCT-A and -B, the line-tracing test, the serial-dotting test and the DST (PSE-Syndrome-Test) is recommended.

Table 3 : Commonly used psychometric tests [11]

Pschometric tests	Measure
WAIS – Performance	Nonverbal skills (performance intelligent quotient)
1. Digit symbol	Motor speed and accuracy, short time visual memory
2. Block design	Visual spatial motor functioning
3. Picture completion	Basic perceptual and conceptual skills as
4. Picture arrangement	assessed through visual recognition and
5. Object assembly	identification
Trail making tests	Visuo-spatial orientation, motor speed, concentration
1. Number connection test A	and attention
2. Number connection test B	
3. Figure connection test A	
4. Figure connection test B	
Canceling A's test	Preattentive visual processing
Digit span	Attention
Line tracing test	Visuo-motor co-ordination and psychomotor slowing
Serial dotting test	Motor speed and co-ordination
Simple reaction time to light	Motor speed and co-ordination
Simple reaction time to sound	Psychomotor speed in response to sound
Choice reaction time to light	Psychomotor speed in response to a light or a sound
Choice reaction time to sound	stimulus when either stimulus may occur, also evaluates decision making time

2. ELECTROPHYSIOLOGICAL OR NEUROPHYSIOLOGICAL TESTS

Due to the disadvantages and the difficulties in interpretation of neuropsychological tests, the use of electrophysiological methods has been proposed as a more objective and specific method for the assessment of MHE. Although EEG is the most widely used neurophysiological diagnostic tool for the detection of clinically apparent HE, its diagnostic role in MHE is minor.

With a percentage of abnormal examinations ranging between 8%-35% among cirrhotics without overt HE, it is considered less sensitive than psychometric tests, and its

changes are not specific, as in other metabolic encephalopathies. Additionally, psychotropic agents can induce similar alterations. For diagnosis of MHE, an elevated percentage of this activity is necessary. Quantitative and automated .spectral. EEG analysis is preferable to visual EEG analysis for the assessment of MHE, because it integrates the tracing and delineates the dominant signals.

Electroencephalogram (EEG)

EEG can be assessed by means of simple visual reading and by quantitative methods such as spectral analysis. EEG is best assessed using spectral rather than visual analysis because its repeatability is greater. An objective classification of EEG alterations in HE, which was based on
EEG parameters obtained by automatic quantitative spectral analysis, was proposed more recently by Van der Rijt et al [9]. Such a technique increases the reliability of
EEG assessment. In the absence of other causes, the alterations observed in the EEG in cirrhotic patients are assumed to reflect the presence of MHE, since they roughly correlate with plasma ammonia concentrations and other indices of hepatic dysfunction and predict the development of overt HE and liver related death, at least in patients with advanced liver disease.

Apart from EEG, several investigators have used evoked potentials (EP) such as the P300 (P300 event related potentials), the SSEP (somatosensory-evoked potentials), the BAEP (brain stem auditory-evoked potentials) and the VEP (visual-evoked potentials) with a reported rate of abnormal findings in cirrhotics without overt HE ranging between 14%-78%, 5%-34%, 0%-41% and 0%-63% respectively. With the exception of P300, their

sensitivity is unsatisfactory compared to that of psychometric tests and the specificity cannot be fully determined.

Several parameters can be determined for the interpretation of their results that are expressed as time (in milliseconds) to positive or negative deflections, including peaks and latencies. In clinical practice, EP is not widely used because of the need for sophisticated equipment and neurophysiological knowledge.

The P300 examination is an endogenous EP that is regarded as representing stimulus evaluation processes. In contrast to the conventional EPs, the response on P300 does not depend on the physical properties of the stimulus, but rather on the meaning of the stimulus to the patient. In this test, the response to two different stimuli, visual and acoustic, is measured and the patient is asked to identify
a predefined stimulus. A minimal hepatic encephalopathy prolongation of the P300 latency to acoustic stimuli is observed in patients with MHE.

The Consensus conference of the 11th World Congress
Of Gastroenterology proposed: .When it is possible, quantitative neurophysiologic tools (like EEG with mean dominant frequency, P300 auditory evoked potentials) should be used.

Event Related (Cognitive) Evoked Potentials

There are two kinds of evoked potentials, i.e., exogenous evoked potentials and endogenous event related potentials.

Event related endogenous potentials occur secondary to the stimulus processing response. They occur independent of the type of stimulus, and are a measure of the cognitive function responsible for processing the response to a stimulus. Therefore these tests are sensitive in detecting subtle cognitive deficits, which are an integral part of the early stages of HE. Tests are carried out by giving either auditory or visual stimuli.

Two types of stimuli are used, the “common or the frequent stimuli” interspersed randomly which the “target or rare stimuli” in ratio of about 80:20 respectively. The patient is asked to concentrate on the target stimuli only and
register them by counting or indicating in some way. Potentials occurring in response to this process are recorded. The event related P300 wave is the most consistent wave and can be considered the electrophysiological counterpart of the psychometric tests as both involve active use of the cognitive faculties.

Saxena et al [6] showed P300 was altered in 20-80% of cirrhotic patients with no clinical evidence of HE or with grade I changes. They also demonstrated, in a follow up study that changes in P300 latency predicted the occurrence of overt HE.

Critical Flicker Frequency

Other methods applied for detection of MHE include measuring of the CFF threshold at which light pulses are perceived as fused. Kircheis et al [12] evaluated CFF in 92 patients

with cirrhosis. The investigation is based on the suggested pathogenesis of HE, that low-grade astrocyte swelling is an early event and triggers HE by altering the glioneural communication. The authors
based their study on the hypothesis that retinal gliopathy could serve as a marker of cerebral gliopathy in HE. They also performed psychometric tests in these patients.

The authors defined a cut-off between normal and pathologic CFF of 39 Hz. Using this frequency as cut-off, CFF analysis detected MHE in about 30% of cirrhotic patients compared with about 50% with psychometric tests. Authors recommended CFF as a simple and reliable test for the diagnosis of MHE after considering long time spent with psychometric tests. However, approximately 40% of the patients who were classified as MHE by the psychometric tests had normal CFF. Therefore, CFF
alone may not be adequate for the detection of MHE. Further studies are required in this field to confirm the efficacy of this test and its value in relation to psychometry and other neurophysiological tests.

Table 4 : Neurophysiological methods [11]

1. ***Electroencephalogram (EEG)***
    a. Standard
    b. Mean dominant frequency

2. Evoked potentials

    a. Exogenous
        i. Brainstem auditory evoked potentials (BAEP)

ii. Visual evoked potentials (VEP)

iii. Somatosensory evoked potentials (SSEP)

b. Event related potentials (P300)

i. Visual paradigm

ii. Auditory paradigm

3. ***Critical flicker frequency (CFF)***

3. NEUROIMAGING TESTS

Brain imaging provides no useful information for the Assessment of MHE.

Computer tomography must be used only for differential diagnosis. Although cranial magnetic resonance imaging shows characteristic abnormalities in cirrhotic patients (symmetric pallidal hyperintensities in T1-weighted images), these changes do not correlate with the grade of encephalopathy.

Proton magnetic resonance spectroscopy and positron emission tomography (PET) are two relatively new imaging methods and the experience in diagnosis of MHE with these is very limited.

4. TEST OF CEREBRAL METABOLISM

There is a very little data about tests of cerebral Metabolism in the diagnosis of MHE. Clinical significance of MHE.

Impact on daily life:

The significance of MHE diagnosis is still a subject of debate. Several investigators have reported a negative influence on daily functioning.

Other studies suggest a possible relation between MHE and the subsequent development of episodes of overt HE. The reduction in the ability of these patients to carry out activities (driving a car, performing at work) probably reflects the neuropsychological deficits founded in MHE. It has been reported that a percentage of between 44% and 70% of cirrhotics with the diagnosis of MHE show an impairment in their ability to drive an automobile. On the other hand, other investigations did not revealed differences in quality of automobile driving between cirrhotics with MHE and healthy subjects.

Quality of life:

Patients with MHE experience a poor quality of life with serious difficulties in sleep, hobbies, recreation and deterioration of body care. The performance of SIP (Sickness Impact Profile) questionnaires showed Highest scores on the areas of social interaction, alertness, Emotional behavior, mobility, sleep/rest, home management and recreation and pastimes. Sleep abnormalities are frequent in all cirrhotics and may be related to alterations of circadian function, or could reflect anxiety and depression as a result of living with chronic disease.

The prognostic value of MHE:

The clinical repercussions Of detecting MHE are still unknown. A possible prognostic value of psychometric alterations in the subsequent development of overt HE and survival is suggested by several authors, but very few studies can confirm these statements. Most of these have been limited to patients with advanced liver disease (portal systemic shunts, decompensated cirrhosis) and the follow up time was very short: less than 12 months. Only two long term follow up studies have confirmed that MHE is an independent risk factor for the development of HE.

The predictive value of MHE on survival is also a subject of debate and the relationship between severity of liver disease and psychometric alterations is not yet clarified.

Diagnosis of MHE

Various tools have been evaluated for the correct diagnosis of MHE and include the psychological tests, neurophysiological tests, regional cerebral blood flow changes and magnetic resonance spectroscopy. However, in the absence of a "*gold standard*" psychometric and Neurophysiological methods have been the most trusted and widely used tests. Combination of at least two psychometric (trail making tests, block design or digit symbol test) and one neurophysiological test (P300 BAEP or electroencephalography with mean dominant frequency) appears to be optimal in detecting MHE.[10, 11]

Diagnostic tools for MHE

There are numerous modalities, which are used to diagnose MHE .[66] However traditionally the diagnosis has been limited to the presence of neurological impairment demonstrated by neuropsychological assessment or neurophysiological tests .[10,11,66]

Table 5: Diagnostic methods for MHE[66]

Methods	Advantages	Disadvantages
Neuropsychological assessment	Better recognition of clinical significant	Subjective Time consuming
Psychometric hepatic encephalopathy score (PHES)	Easy to use	Few validating studies ? Learning effect
Neurophysiological tests(EEG, spectral EEG, evoked potential)	Objective tests Useful for repeated testing	Equipments required Lack of information on behavioral consequences
computerized tests (Critical flicker frequency, reaction time)	Easy to apply	Insufficient studies

Diagnostic criteria for MHE

1. Confirmation of a disease that can cause MHE

   Cirrhosis

   Other: congenital portosystemic shunts, portal thrombosis.

2. Normal mental status on clinical examination

   Absence of signs of overt encephalopathy; dysarthria, ataxia, flapping tremor, disorientation, obvious slow mental processing

3. Documentation of neurological impairment by

   Formal neuropsychological assessment

   Short neuropsychological battery

   Computerized tests

   Neurophysiological tests

4. Exclusion of other disturbances that may cause the neurological impairment

   Research studies: exclusion of participants with confounding factors (active alcoholism, visual impairment, co morbidities, etc.)

   Clinical practice: judgment of the effect of confounding factors.

Treatment of minimal hepatic encephalopathy

The pathogenesis of MHE is thought to be similar to that of overt HE and ammonia plays a key role.[12-14] Ammonia induced alterations in cerebral blood flow and glucose metabolism have shown that there is a significant decrease of glucose utilization of various cortical regions that correlate with the patients cognitive functions.[14] Various treatment modalities have been tried to treat this condition e.g., dietary protein manipulation, [15] branched-chain amino acids, [16] L–ornithine L aspartate,[17] and lactulose.[4, 18, 19] Most of these therapies were aimed to reduce ammonia levels.

Non absorbable disaccharides:

Lactulose is the most common agent used in the treatment of MHE. Treatment with lactulose is of benefit in majority of patients with MHE.[4, 18,19] Watanabe et al showed that MHE disappeared in 50% of pts treated with lactulose for 8 weeks but persisted in 85% of untreated pts.[19] We found marked improvement in psychometric tests with lactulose administration for 3 months; MHE disappeared in 8/10 patients on lactulose but persisted in all 8 untreated patients.[18] Lactulose lowers ammonia levels by alteration in gut flora resulting in decreased production and absorption of ammonia.

Dhiman and co-workers for the first time investigated the effect of treatment related improvement in cognitive functions on health related quality-of-life (HRQOL).[4] We measured psychometric performance by number and figure connection tests A and B, picture completion and block design tests, and HRQOL by Sickness Impact Profile (SIP) in 90 cirrhotic patients at inclusion into the study and 3 months thereafter.

Sixty-one (67.7%) patients had MHE. They were randomly assigned in a 1:1 ratio to receive treatment (lactulose) for 3 months (n=31) or no treatment (n=30) in a non-blinded design. Mean number of abnormal NP tests decreased significantly in patients in treated group compared with patients in untreated group (MANOVA for time and treatment, *P* =.001). Intention to treat analysis showed that improvement following lactulose therapy was significant. While 20 out of 31 (64.5%) patients in treated group improved, 2 of 30 (6.7%) patients did so in untreated group (Fisher's exact test; $P < .0001$). Mean total SIP score improved among patients in the treated group compared with patients in untreated group (MANOVA for time and treatment, *P*=.002). Improvement in HRQOL was related to the improvement in psychometry. Thus treatment with lactulose improves both cognitive functions and HRQOL in cirrhotic patients with MHE.

Table 6: Treatment with lactulose

Author (year)	MHE (N)	Duration of treatment	Result
Wantabe et al (1997)	36 Lactulose 22 Placebo 14	8 weeks	Lactulose better than placebo
Dhimen et al (2000)	26 Lactulose 14 Placebo 12	3 months	Lactulose better than placebo
Zeng et al (2003)	60	8-24 weeks	Lactulose better than placebo
Prasad et al (2007)	61 Lactulose 31 Placebo 30	3 months	Lactulose improves cognitive and SIP score

Prebiotics and Synbiotics

Treatment with synbiotics (probiotics and fermentable fiber) has been suggested but not assessed in controlled studies in the treatment of MHE. Liu et al [3] reported an alternative and novel approach of modulating the gut micro ecology and acidifying the gut lumen for therapeutic benefit in cirrhotic patients with MHE by treatment with synbiotics. The investigators of this study have attempted to confirm the usefulness of synbiotics in the treatment of MHE. They screened 97 consecutive cirrhotic patients without overt hepatic encephalopathy (HE) for MHE using the number connection test (NCT) and measurement of BAEP.

MHE, defined by abnormality of at least one test modality, was seen in 58 (60%) patients. Fifty-five of them MHE were randomized to receive a synbiotic preparation i.e., a probiotic plus fermentable fiber
(n=20), fermentable fiber (n=20), or placebo (n=15) for 30 days. Probiotic compound consisted of 4 freeze-dried, non-urease-producing bacteria, namely *Pediacoccus pentoseceus*, *Leuconostoc mesenteroides*, *Lactobacillus paracasei* subspecies *paracasei* 19 and Lactobacillus *plantarum* 2592, each at dose of 1010 colony forming units per sachet.

Fermentable fiber consisted of beta glucan, 2.5 g; insulin 2.5 g, pectin 2.5 g, and resistant starch, 2.5 g. Placebo consisted of wheat based nonfermentable fiber. Patients were evaluated with NCT and BAEP, serum ammonia and endotoxin levels, and stool quantitative bacteriological analysis at study entry, after 1-month of treatment and again after 14 days. Cirrhotic patients with MHE had substantial derangements in the gut micro ecology, with significant fecal overgrowth of potentially pathogenic *Escherichia coli* and *Staphylococcal* species.

Synbiotic treatment significantly increased the fecal content of non-urease-producing *Lactobacillus* species at the expense of these other bacterial species. The effect persisted at reassessment 14 days after cessation of supplementation. Such modulation of gut flora was associated with a significant reduction in blood ammonia levels and reversal of MHE in 50% of patients. Synbiotic treatment was also associated with a significant reduction in endotoxemia.

The Child-Turcotte-Pugh functional class improved in nearly half of patients. Similar benefit was observed with fermentable fiber alone in a substantial proportion of patients. It may be concluded that the treatment with synbiotic or fermentable fiber is an alternative to lactulose for management of MHE in patients with cirrhosis. Shall we routinely screen cirrhotic patients for the presence and treatment of MHE [59] Recently published literature favors it.

S. K. Sarin et al[20] (2007) studied156 cirrhotic patients (age 41 ± 12.5 yr) without overt encephalopathy were evaluated by psychometric (number connection tests A, B or figure connection tests A, B), P300 auditory event related potential (ERP) and CFF. MHE was diagnosed by abnormal psychometric and/or P300 auditory event related potential. Prevalence of MHE was 53% with 27 (43%) in Child's A, 33 (59%) in Child's B and 23 (62%) in Child's C cirrhosis (*p* = NS). Of 83 patients, 72 (87%) had abnormal psychometry, 64 (77%) had abnormal P300 auditory event related potential (ERP) (380.6 ± 28.8 ms) and in 66 (80%) CFF was below 39 Hz. 60 (83%) patients with abnormal psychometry and 51 (80%) with abnormal P300 auditory event related potential had CFF below 39 Hz. CFF sensitivity (96%), specificity (77%) and positive predictive value (68%), negative predictive value (98%) and diagnosis accuracy was 83.3% when compared to patients with both abnormal psychometry and P300 Event Related Potentials Critical flicker frequency is a simple, reliable and accurate test without any age or literacy dependence for the diagnosis of MHE.

Schomerus *et al*[21] *(2008)* conducted the neuropsychological function testing in 292 liver cirrhosis patients without overt hepatic encephalopathy and then assessed them in regard to fitness to drive. He developed an easily conducted computer-aided quantitative neuropsychological function test system for use in routine medical practice. The system was used prepare basic values according to age in 542 healthy subjects and the results were compared with 292 liver cirrhosis patients.

The software is composed of eight tests: Number Connection Test -A, Number Connection Test -B, Figure Design Test, Digit Symbol Test, Block Design Test and the Reaction Time-A, Reaction Time-B and Reaction Time-C.

The results showed that 60% of the patients were unfit to drive a motor vehicle. The results also showed that 25%of the patients were capable of limited driving only. The investigators also found significantly more persons unfit to drive in an alcoholic liver cirrhosis group than in a non-alcoholic liver cirrhosis group.

K. Dhiman et al[22] (2004) screened 97 consecutive cirrhotic patients without overt hepatic encephalopathy (HE) for MHE using the

- number connection test (NCT) and
- measurement of brainstem auditory evoked potentials (BAEP).

The cause of cirrhosis was hepatitis virus B or C in

75 (77%) patients, alcohol in 19 (20%) and other in 3 (3%). Patients with alcoholic hepatitis were carefully excluded.

He concluded that Combination of at least

- 2 psychometric

(trail making tests, block design or digit symbol test) and

- 1 neurophysiological test

(P300 BAEP or electroencephalography with mean dominant frequency)

seems to be optimal in detecting MHE in cirrhosis patients. **M.F. El-Shater et al[23] (2007)** studied 43 well-compensated cirrhotic patients without signs of encephalopathy were studied by neuropsychological cognitive test battery, P300 ERP latency, EEG, conventional MRI brain. The patients were followed-up for 2 yrs. to monitor subsequent episodes of overt encephalopathy. Child-Pugh classification was done throughout the study to assess severity of liver cirrhosis. Forty-six healthy subjects, age, sex and education matched, served as a control group.

Minimal HE was diagnosed in 21(48.8%) out of 43 cirrhotic patients. Inverted sleep rhythm was reported in 85.7%, of cirrhotic with MHE. Delayed P3ERP latency was seen in 38.1% of cirrhotic patients with MHE, while Number Connection Test (NCT-A & B) times were prolonged in 71.4% of the patients. EEG abnormality was detected in 47.6 %, while MRI signs were reported in 80.9% of cirrhotic with MHE. Out of 43 patients, 18(41.8%) developed overt encephalopathy, 66.7% of the patients with MHE progressed to overt encephalopathy within a mean duration of 9 months, while only 13. 6% of the non-MHE patients did so. Of the patients who developed overt encephalopathy, 83.3% had abnormal EEG, 77. 8 % had abnormal NCT, while 59. 3% had P3ERP latency prolongations.

D. Antonicelli et al[24] (2007) studied 182 consecutive pts, without overt encephalopathy. (142 pts, 97 men and 45 women; age 20-70; 94 Child A, 44 Child B and 4 Child C) only psychometric tests were performed in order to study the prevalence of MHE. The remaining 40 pts (29 men, 11 women; age 20-70; 27 Child A, 12 Child B, 1 Child C), underwent both psychometric and neurophysiological tests (only in ten pts, they performed CFFF). In addition, this group of 40 pts was clinically evaluated by neurologists and oculists, in order to exclude neurological or ocular disease that could have affected neurophysiological tests.

All tests were validated in normal subjects who served as control group. Eighty pts out of 142 (57%) resulted affected by MHE using psychometric tests. By intention to treat analysis, in the remaining 40 pts they obtained the following results: abnormal psychometrics in 21 patients (52.5%), abnormal BAEP in 19 patients (47.5%), abnormal

CFFF in 7 out of 10 patients (70%) Neurophysiological tests, in particular CFFF, ameliorate the diagnostic sensitivity for MHE.

M L Zeneroli et al [25] (1984) , studied visual evoked potential recordings in 45 liver cirrhosis patients with (n = 29) and without (n = 16) encephalopathy, in 15 normal volunteers, and in one patient with an opioid induced stupor state. Visual evoked potential parameters were classified on the basis of EEG recordings. Plasma concentrations of amino acids, octopamine, and ammonia were assayed in order to document the metabolic change of hepatic encephalopathy. Latencies and wave patterns recorded after flash stimulation differentiated the four degrees of the coma one from another according to EEG classification in the 29 patients with encephalopathy.

In the group of 16 patients without clinical and EEG evidence of encephalopathy the visual potential recordings discriminated a group of patients (n = 10) in a preclinical stage of encephalopathy. Biochemical parameters and subsequent clinical observation of patients confirmed our judgment of a preclinical stage of encephalopathy. These results suggest that visual evoked potentials are a simple, suitable and objective method for differentiating the degrees of encephalopathy and for identifying the preclinical stage of encephalopathy.

M. G. Davies et al [26] (1990), studied the value of the flash visual evoked response (VER) in patients with MHE. Twenty-six controls and 21 non-encephalopathy and 12 encephalopathy (grade 1/ 2), biopsy-proven, cirrhotic patients were assessed clinically, psychometrically, and electro physiologically. Flash VER from three different leads were obtained from each patient. Data from the fronto-occipital leads gave the best differentiation between the subjects.

The P2 and N3 peak latencies were significantly increased in the two liver groups and correlated with the mental state and psychometric results. The N3 latency had a 92% specificity and a 50% sensitivity in the detection of grade 1/2 HE. This study suggests that the N3 latency changes may be a good marker of early clinical HE and useful in the longitudinal assessment of individual patients.

Neville L. Sandford et al[27] (2005), studied Thirty-six patients with advanced chronic liver disease of predominantly alcoholic etiology and with a documented history or current physical evidence of hepatic encephalopathy were studied and compared to 30 healthy controls. Assessment was made of their mental state, number connection test, venous blood ammonia, electroencephalography and visual evoked potentials with both pattern reversal and flash stimuli.

Because of considerable inter- and intraindividual variation in waveform, visual evoked potentials from flash stimuli were considered unreliable. In pattern reversal visual evoked potentials, the latency of the N_1 and P_1 waves was significantly longer ($p < 0.05$) in patients than in controls; however, the wave latencies did not correlate with the mental state score. The mental state score correlated with the number connection test ($r = 0.69$, $p < 0.001$), asterixis ($r = 0.36$, $p < 0.05$), electroencephalography mean dominant frequency ($r = 0.44$, $p < 0.01$) and blood ammonia ($r = 0.60$, $p < 0.01$).

In 14 patients studied sequentially, change in the mental state score correlated with change in the number connection test ($r = 0.80$, $p < 0.01$) and asterixis ($r = 0.75$, $p < 0.01$) but not with change in the electroencephalography, blood ammonia or visual evoked potential wave latencies. Although visual evoked potentials are abnormal in patients with alcoholic cirrhosis and encephalopathy, they are less accurate in assessing the level of consciousness than simple bedside evaluation with a number connection test.

Parampreet S Kharbanda et al[28] (2003) studied cognitive deficits found on neuropsychological and/or neurophysiologic methods in patients with liver disease, present most commonly in cirrhosis. Patients suffering from MHE may have psychomotor slowing and cognitive deficits affecting their ability to perform many activities of daily life, especially driving and other activities requiring subtle cognitive abilities. It has been now been shown that patients with MHE improve after treatment with agents like lactulose and other therapeutic interventions.

Neuropsychological and neurophysiologic tests have been widely used and have shown the greatest promise for the detection of MHE. Commonly used psychometric tests include trail making tests (number and figure connection tests) and Wechsler Adult Intelligence Scale (WAIS) for verbal and performance skills. Among the various neuropsychological or psychometric tests, trail making tests and block design and digit symbol tests from WAIS-performance battery appear to be adequate for diagnosis of MHE.

Standardized tests including NCT A and B, line tracing, serial dotting test and digits-symbol test (PSE syndrome test) validated in German patients need validation in other populations. Both exogenous evoked potentials and endogenous event-related potentials have been used extensively in diagnosing MHE. However, the event-related P300 wave is the most consistent wave and can be considered the electrophysiological counterpart of the psychometric tests as both involve active use of the cognitive faculties. Other new tests like the critical flicker frequency have shown some promise but further studies are required to substantiate initial results.

In conclusion, a combination of at least two psychometric (trail making tests [NCT or FCT], block design and digit symbol test) and neurophysiological tests (P300 auditory evoked potential or electroencephalography with mean dominant frequency) appears to be optimal in detecting MHE.

M. Senzolo et al[29] (2004) studied 114 patients, (aged 58,2±8,5 years) with liver cirrhosis they underwent PSE (digit symbol test, trail making A and B, serial dotting and line tracing test, single test score +1,-3) to classify patients with MHE (total score<-4). Neurophysiological evaluation was performed with spectral quantitative EEG (sEEG) with

relative band power calculation. and analysis of interpeak latency of evoked potential wave P300. pNH3 (x10–5mmHg), venous and arterial levels of ammonia were also assessed.

PSE score revealed MHE in 3/14 patients and sEEG alteration seen in 6/14 patients (2/6 with also pathological PSE score). Length of interpeak latency P300 was pathological in 1/14 patients. No correlations between P300, sEEG and PSE were seen. pNH3 levels were significantly higher in patients with sEEG alteration (p<0,01). pNH3 and arterial ammonia correlated with theta band increase in sEEG. pNH3 did not correlate with pathological PSE score or P300 wave abnormalities.

sEEG, that correlates with pNH3 levels, but not with arterial or venous ammonia concentrations, seems to be a useful tool to diagnose cerebral function alterations in cirrhotic patients without overt EPS. PSE Syndrome Test and P300 seem to be less useful compared to sEEG in diagnosing MHE.

Jasmohan S. Bajaj et al[30] (2008) studied the reliability and validity of Inhibitory Control Test (ICT) for MHE diagnosis. ICT was compared with a psychometric battery (standard psychometric tests [SPT]) for MHE diagnosis and overt hepatic encephalopathy (OHE) prediction. ICT was administered twice for test-retest reliability, before/after transvenous intrahepatic portosystemic shunting (TIPS), and before/after yogurt treatment. The time taken by 2 medical assistants (MA) to administer ICT was recorded and compared with that of a psychologist for cost analysis.

136 cirrhotic patients and 116 age/education-matched controls were studied. ICT (>5 lures) had 88% sensitivity for MHE diagnosis with 0.902 area under the curve for receiver operating characteristic. MHE-positive patients had significantly higher ICT lures (11 vs 4, respectively, *P* = .0001) and lower targets (92% vs 97%, respectively, *P* = .0001) compared with MHE-negative patients. The test/retest reliability for ICT lures (n = 50, r = 0.90, *P* = .0001) was high. ICT and SPT were equivalent in predicting OHE (21%). ICT

lures significantly worsened after TIPS (n = 10; 5 vs 9, respectively; *P* = .02) and improved after yogurt supplementation (n = 18,

10 vs 5, respectively; *P* = .002). The MAs were successfully trained to administer ICT; the time required for test administration and the associated costs were smaller for ICT than for SPT. Concluded that ICT is a sensitive, reliable and valid test for MHE diagnosis that can be administered inexpensively by MAS.

Piero Amodio et al[31](2008) studied patients by using Psychometric Hepatic Encephalopathy Score (PHES) and EEG to detect minimal hepatic encephalopathy (MHE). They aimed at standardizing PHES in Italy and comparing Italian, German and Spanish norms in EEG characterized cirrhotic patients.

PHES was standardized on 228 normal individuals. Repeatability was studied in 128 individuals. One hundred patients with liver cirrhosis underwent EEG and PHES which was computed on the Spanish, German and the Italian norms.

Age and education levels were predictors of psychometric tests; therefore, adjusted Z scores were calculated. Practice effect ($p < 0.01$) was detected. In the patients, the Italian norms were closer to the Spanish norms (difference _0.14 ± 1.32, $p = 0.29$) than to the Germans ones (difference 1.97 ± 2.07, $p < 0.001$). The PHES calculated on the Italian norms was correlated with the EEG mean dominant frequency more closely than the ones calculated on the German and Spanish norms ($r = 0.38$, $r = 0.31$, $r = 0.33$, respectively – $p < 0.01$). The detection of MHE on the basis of PHES and EEG showed limited agreement (73%, Cohen's K = 0.32).Different findings between PHES and EEG possibly reflect various features of MHE.

Andrzej Habior et al[32] (2009) In patients with liver cirrhosis, minimal hepatic encephalopathy (MHE) is associated with a poor quality of life and difficulty in driving. It has also been suggested that MHE can precede the development of overt hepatic encephalopathy (OHE). No gold standard exists to detect MHE. Therefore the prevalence of this entity varies depending on the diagnostic methods used.

51 patients with liver cirrhosis and portal hypertension (29 with primary biliary cirrhosis, 22 with HCV infection) were studied. In all patients they performed seven diagnostic tests: four psychometric tests (NCT-A, NCT-B, DST, BDT), EEG, spectral EEG, P300 auditory event related potential, critical flicker frequency (CFF), proton magnetic resonance spectroscopy of the brain (1HMRS) and serum concentration of astroglial protein S100□.Patients were followed up for a period of 4 years.

Based on the psychometric tests, 9 out of 51 patients (17.6%, 95% CI 7-28) were diagnosed to have MHE. If the results of EEG, P300 and spectral EEG were added, the prevalence of MHE raised to 16 of 51 patients (31.3%, 95% CI 18-44). Addition one nonstandard test (CFF, 1HMRS or S100) raised the percentage of patients suspected of MHE to above 40%.

During follow up OHE developed in 14 patients but MHE in this group was earlier diagnosed using psychometric tests in only 10 patients. Twelve of 14 patients with OHE had at least one abnormal result out of the seven tests. Multiple proportional hazard regression model showed a higher risk of OHE in patients with abnormal EEG (HR - 8.4, 95% CI 2.6 -27.3, $p < 0.001$). Other factors, including psychometric and standard and nonstandard tests, did not predict the OHE. Diagnosis of minimal hepatic encephalopathy needs further standardization. Among
the seven different diagnostic methods, only EEG has a predicting value for minimal hepatic encephalopathy in cirrhotic patients.

MATERIALS AND METHODS

The centre of study was Department of Medical Gastroenterology, Madras Medical College and Government General Hospital, Chennai.

Study Design : Prospective study

Venue : Government General Hospital, Chennai

Duration : From January 2008 to December 2008 (12 months)

Collaborating Department : Department of Neurology,
Government General Hospital, Chennai.

Fifty patients who attended Medical Gastroenterology outpatient department with a clinical diagnosis of cirrhosis of liver by clinical, radiological and laboratory parameters included in the study.

Patient selection

Inclusive criteria

1. Patients with a clinical diagnosis of cirrhosis of liver of any etiology.
2. Patients with Child class A.
3. Patients with no clinical evidence of encephalopathy.

Exclusion criteria

1. Patients with Child class B and C
2. Uneducated patients who are unable to perform NCT
3. Patients with overt encephalopathy
4. Severe hypertension
5. Heart disease
6. Diabetes
7. Cerebrovascular and other brain diseases
8. Respiratory failure
9. Renal failure
10. Psychiatric diseases

Protocol

1. All patients who met the above criteria were included in the study and got admitted in our department.
2. The following were noted in each patient

(i) Age

(ii) Sex

(iii) Educational status

(iv) Duration of abdominal distension

(v) H/o Swelling of legs + / -

(vi) H/o Jaundice

(vii) H/o of G. I. Bleed

(viii)

(ix) H/o altered sleep rhythm

(x) H/o Bleeding tendencies (epistaxis, gum bleeding, hematuria etc)

(xi) H/o Abdominal pain

(xii) H/o Breathlessness on exertion

(xiii) Past H/o jaundice

(xiv) Past H/o blood transfusions

(xv) Past H/o tattooing

3. A thorough physical examination was done in all the fifty patients. Signs of chronic liver disease with portal hypertension like palmar erythema, spider nevi, gynaecomastia, large abdominal wall collaterals (caput medusa), fetor hepaticus and asterixis were noted.

Examination of central nervous system was done in detail.

Investigations

The following investigations were done in all fifty patients.

1. Liver function tests including Prothrombin time / INR
2. Ultra sonogram of the abdomen
3. Diagnostic upper G. I. Endoscopy
4. NCT done at the bedside
5. Electroencephalogram
6. Brainstem auditory evoked potential

Number Connection Test:

After admission in the ward patients were given the Reitan's trail marking chart [80] and asked to connect the numbers in an orderly manner and the time taken to complete the test was recorded. Patients with normal mental function will complete the

test within 90 seconds, hence the test is considered abnormal if the patient is not able to complete the test within 90 seconds.

Reitan's trail making chart

Electroencephalogram (EEG) and Brainstem auditory evoked potentials (BAEP) were done for all patients in the department of Neurology, Government general hospital, Chennai itself and findings were collected and recorded.

Fig 2: Nicolet Bravo EEG

Results

Thirty four male (68%), 16 (32%) female patients, mean age was 45.6 years. All of them are Child A class functional status patients. Ethanol related cirrhosis in 29 patients (58%), Post necrotic (HBV related) cirrhosis in 7 patients (14%), Cryptogenic cirrhosis in 14 patients (28%), Number connection test (NCT) was abnormal in 24 patients (48%), 15 patients had abnormal Electroencephalogram (EEG) suggestive of diffuse bilateral cerebral dysfunction (30%), 12 patients had abnormal brainstem auditory evoked potentials (BAEP) in the form of abnormal prolongation of latency and asymmetry (24%), 7 Patients had both abnormal NCT and EEG (14%), 7 Patients had both abnormal NCT and BAEP (14%), 6 Patients had both abnormal EEG and BAEP (12%), Only 3 patients had abnormal NCT, EEG and BAEP (6%), About 2/3rd of the patients were males (68%). Abnormal tests found in 42% of patients in the age group 40- 50years, 28% of patients in the 30-40 years age group, 20 % of patients in 50-60 years age group, only 8% in 60-70years age group and only one patient (2%) in 70-80 years age group.

DISCUSSION

About one hundred (100) articles have been published in various national and international journals about the importance of Number connection test (NCT), Electroencephalogram (EEG) and Brainstem auditory evoked potentials (BAEP) to find out the prevalence of minimal hepatic encephalopathy.

In this study 64% of patients had minimal hepatic encephalopathy detected by either abnormality in single test alone [abnormal NCT alone (48%) or EEG alone (30%) or BAEP alone (24%)] or combination of 2 abnormal tests (20 patients (40%) had abnormality in two tests) or three abnormal tests (3 patients (6%) had abnormality in all the three tests), NCT alone is abnormal in 48% of patients, EEG was abnormal in 30% of patients and BAEP was abnormal in 24% of patients, this prevalence is more than that observed in S.K. Sarin study (2007),wherein the prevalence was only 73% and abnormal psychometric test was seen in 87% of patients, abnormal event related potential in 77% of patients when comparing this study it is almost two to three fold increased incidence this may be due to inclusion of Child B and C patients in their study.

Prevalence of MHE using EEG in this study is 30%, it is similar to the study by Groenweg (2000) - 27%. Prevalence of MHE in this study using BAEP is only 24%, it is much lower when comparing other studies, Yen et al (1990) – 60%, Lin et al (2004) – 60% this difference is probably due to inclusion of patients with Child B and C in their studies.

Another study by Schomerus (2008) showed 60% of patients had minimal hepatic encephalopathy in the form of poor driving skills most of them had ethanol related cirrhosis, similarly in this study also 58% of patients had ethanol related cirrhosis, 28% had cryptogenic and 14% had HBV related cirrhosis.

When comparing available studies with this study in relation to etiology of cirrhosis most common etiology in other studies is virus related either HBV or HCV in 77% of patients in Dhiman et al (2004) but in this study ethanol is being the most common etiology with the peak incidence of age distribution is between 40 – 50 years age group, this is because cirrhotics with viral etiology coming for treatment late with severe disease unlike ethanol related cirrhotics. In Akinobu Kato et al (2008) series etiology of cirrhosis viruses both HBV and HCV in 81%, Ethanol in 13% and other causes in 6% of patients

In this study age group between 40-50 years has the highest prevalence of MHE it is 42%, followed by 28% in the 30 -40 years group, and then 20% in the 50 -60years group. But in the study by Akinobu et al (2008) highest prevalence of MHE in the age group between 60-64 years (28%), in the 65-69 years age group prevalence is 28%, lowest prevalence of 5% in 40-44 years group, probably this may need more sample size to analyze that age group difference.

In this study sex distribution is males 34 (68%) and female 16 (32%), sex distribution is similar to Akinobu Kato study (2008) wherein male 66% and female 34%. Prevalence of MHE using NCT in this study is 48%, is similar to other available studies Yen et al (1990) - 60%, Lin et al (2004) - 60%, Sharma et al (2007) – 53%, Groenweg et al (2000) – 27%, Das et al (2001) – 63%, Prasad et al (2007) – 68%.

CONCLUSION

Minimal Hepatic Encephalopathy is proved undoubtedly impairs quality of life observed in patients with cirrhosis who have no overt encephalopathy, medical intervention can improve both cognitive function and health related quality of life.

Hence screening for Minimal Hepatic Encephalopathy is important in cirrhotics to provide them a good quality of life, driving skills which is impaired in Minimal Hepatic Encephalopathy by interfering at the early stage of the disease to prevent progression to overt encephalopathy which has got a high mortality.

Diagnosis of MHE requires high index of suspicion, useful three diagnostic tools are NCT, EEG and BAEP. This study showed 48% had abnormal NCT, 30% had abnormal EEG, 24% had abnormal BAEP with combined prevalence of MHE 64%.

This study suggested that Number connection test (NCT), Electroencephalogram (EEG) and Brainstem auditory evoked potentials (BAEP) are valid tools for the screening of minimal hepatic encephalopathy in cirrhotic patients of various etiology as there is a greater likelihood of overt encephalopathy development in the immediate follow up period in patients with an abnormality detected by these tests than in patients with no such abnormality.

Seven patients developed overt encephalopathy within a period of 2months in the one year follow up period. Large scale study may be needed to enlighten these aspects. These tools can be used for screening for MHE in patients with cirrhosis.

Bibliography

1. Liu Q, Duon ZP, Ha DK et al. Symbiotic modulation of gut flora: effect on minimal hepatic encephalopathy in patients with cirrhosis. Hepatology 2004; 39:1441-49

2. Dhiman RK, Chawla YK. Minimal Hepatic Encephalopathy: Should we start treating it? Gastroenterology 2004; 127:1855-1857

3. Liu Q, Duon ZP, Ha DK et al. Symbiotic modulation of gut flora: effect on minimal hepatic encephalopathy in patients with cirrhosis. Hepatology 2004;39:1441-49

4. Prasad S, Dhiman RK, Duseja A, Chawla Y, Sharma A, Agarwal R. Lactulose improves cognitive functions and health-related quality of life in cirrhotic patients with minimal hepatic encephalopathy. *Hepatology* 2007;45:

5. Groeneweg M, Quero JC, De Bruijn I, Hartmann IJ, Essink-bot ML, Hop WC, Schalm SW. Subclinical hepatic encephalopathy impairs daily functioning. *Hepatology* 1998; 28:45-49.

6. Saxena N, Bhatia M, Joshi YK, Garg PK, Dwivedi SN, Tandon RK. Electrophysiological and neuropsychological tests for the diagnosis of subclinical hepatic encephalopathy. Liver 2002;22: 190-197.

7. Das A, Dhiman RK, Saraswat VA, Verma M, Naik SR. Prevalence and natural history of subclinical hepatic encephalopathy in cirrhosis. J Gastroenterol Hepatol 2001; 16:531-535.

8. Schomerus H, Hamster W. Quality of life in cirrhotics with minimal hepatic encephalopathy. Metab Brain Dis 2001; 16:37-41.

9. Van der Rijt et al - Objective measurement of hepatic encephalopathy by means of automated EEG analysis. Electroenceph clin Neurophysiol 1984; 57: 423-426.

10. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy- definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. Hepatology 2002; 35:716-721.

11. Kharbanda PS, Saraswat VA, Dhiman RK: minimal hepatic encephalopathy: diagnosis by neuropsychological and neurophysiological methods; Indian J Gastroenterol 2003; 22: {Suppl 2} 537-541.

12. Balata S, Damink SW, Ferguson K, Marshall I, Hayes PC, Deutz NE, et al. Induced hyperammonemia alters neuropsychology, brain MR spectroscopy and magnetization transfer in cirrhosis. Hepatology 2003; 37:931-939.

13. Cordoba J, Alonso J, Rovira A, Jacas C, Sanpedro F, Castells L, et al. The development of low-grade cerebral edema in cirrhosis is supported by the evolution of H-magnetic resonance abnormalities after liver transplantation. J Hepatol 2001; 35:598-604.

14. Lockwood AH, Yap EW, Wong WH. Cerebral ammonia metabolism in patients with severe liver disease and minimal hepatic encephalopathy. J Cereb Blood Flow Metab 1991; 11:337- 341.

15. de Bruijn KM, Blendis LM, Zilm DH, Carlen PL, Anderson GH. Effect of dietary protein manipulation in subclinical portal-systemic encephalopathy. Gut 1983 ; 24:53-60.

16. Egberts EH, Schomerus H, Hamster W, Jurgens P. Branched chain amino acids in the treatment of latent portosystemic encephalopathy. A double-blind placebo-controlled crossover study. Gastroenterology 1985; 88:887-895.

17. Kircheis G, Nilius R, Held C, Berndt H, Buchner M, Gortelmeyer R, et al. Therapeutic efficacy of L-ornithine-L-aspartate infusions in patients with cirrhosis and hepatic encephalopathy: results of a placebo-controlled, double-blind study. *Hepatology* 1997; 25:1351-1360.

18. Dhiman RK, Sawhney MS, Chawla YK, Das G, Ram S, Dilawari JB. Efficacy of lactulose in cirrhotic patients with subclinical hepatic encephalopathy. Dig Dis Sci 2000 ; 45:1549-1552.

19. Watanable A, Sakai T, Sato S et al. Clinical efficacy of lactulose in cirrhotic patients with and without subclinical hepatic encephalopathy. Hepatology 1997 ; 26:1410-14.

20. *S.K. Sarin et al - Journal of Hepatology*, *Volume 47, July 2007*, *Pages 10-11.*

21. Schomerus *et al. Hepatology Research* 2008; 38 (Suppl. 1): S122–S127. 22. K. Dhiman et al – Gastroenterology, Volume 127, Number, December 2004.

23. **M.F. El-Shater et al -** Egypt J. Neurol. Psychiat. Neurosurg., 2007, 44(2): 577-596.

24. D. Antonicelli et al - Digestive and liver disease, volume 40, supplement 1, March 2008, Pages S178-S179.

25. M L Zeneroli et al - *Gut* 1984**;** 25: 291-299.

26. M. G. Davies et al - Scandinavian journal of gastroenterology, Volume 25, Issue 12, December 1990 , pages 1205 – 1214.

27. Neville L. Sandford et al – Hepatology 2005 volume 8, issue 5 AASLD **Pages 1094 – 1098.**

28. Parampreet S Kharbanda et al - Indian J Gastroenterol. 2003 Dec; 22 Suppl 2 :S37-41

29. M. Senzolo et al – journal of Hepatology, volume 40, supplement 1 2004, Pages 72-73.

30. Jasmohan S. Bajaj et al – gastroenterology**,** November 2008, Pages 1591-1600.

31. Piero Amodio et al - Journal of Hepatology 49 (2008) 346–353.

32. Andrzej Habior et al – gastroenterology, volume 136, issue 5, supplement 1, May 2009, Pages A-827.

33. Elsass P, Christensen SE, Mortensen EL, Vilstrup H. Discrimination between organic and hepatic encephalopathy by means of continuous reaction times. Liver 1985; 5:29-34.

34. Nielsen K, Kondrup J, Martinsen L, Døssing H, Larsson B, Stilling B, et al. Longterm oral refeeding of patients with cirrhosis of the liver. *Br J Nutr* 1995;74:55767.

35. Goulenok C, Bernard B, Cadranel JF, Thabut D, Di Martino V, Opolon P, Poynard T. Flumazenil vs. placebo in hepatic encephalopathy in patients with cirrhosis: a meta-analysis. *Aliment Pharmacol Ther* 2002 ; 16:361-7.

36. Cadranel JF, Lebiez E, Di Martino V, Bernard B, El Koury S, Tourbah A, Pidoux B, Valla D, Opolon P. Focal neurological signs in hepatic encephalopathy in cirrhotic patients: an underestimated entity? Am J Gastroenterol. 2001; 96:515-8.

37. Joebges EM, Heidemann M, Schimke N, Hecker H, Ennen JC, Weissenborn K. Bradykinesia in minimal hepatic encephalopathy is due to disturbances in movement initiation. J Hepatol. 2003; 38:273-80.

38. Elsass P, Christensen SE, Mortensen EL, Vilstrup H. Discrimination between organic and hepatic encephalopathy by means of continuous reaction times. Liver 1985; 5:29-34.

39. Ross BD, Jacobson S, Villamil F, Korula J, Kreis R, Ernst T, Shonk T, Moats RA. Subclinical hepatic encephalopathy: Proton MR spectroscopic abnormalities. Radiology 1994 ; 193:457-63.

40. Burra P, Pizzolato G, Orlando F, Rossato A, Chierichetti F, Tedeschi U, Et al. Single-photon emission computed tomography with 99mTC-hexamethylpropyleneamineoxide in cirrhotic patients before and after liver transplantation. Transplant Proc. 1994 ; 26:3677-8.

41. Norenberg, MD. Astrocytic-ammonia interactions in hepatic encephalopathy. Seminars in Liver Disease 1996:16:245-253.

42. Wang V, Saab S: Ammonia levels and the severity of hepatic encephalopathy. Am J Med 2003:114:237-238.

43. Ong JP, Aggarwal A, Krieger D, Easley KA, Karafa MT, Van Lente F, Arroliga AC, Mullen KD. Correlation between ammonia levels and the severity of hepatic encephalopathy. Am J Med. 2003 ; 114:188-93.

44. Clemmensen JO, Larsen FS, Kondrup J. et.al. Cerebral herniation in patients with acute liver failure is correlated with arterial ammonia concentration. Hepatology 1999 ; 29:648-653.

45. Moroni F, Lombardi G, Moneti G, Cortesini C. The release and neosynthesis of glutamicacid are increased in experimental models of hepatic encephalopathy. J Neurochem.1983; 40:850-4.

46. Baraldi M, Zeneroli ML; Experimental hepatic encephalopathy: changes in the binding of gamma-amino bulync acid. Science 1982;216:427-429

47. Zeneroli ML, Baraldi M, Ventura E, Vezzelli C, Tofanetti O, Germini M, Casciarri I. Alterations of GABA-A and dopamine D-2 brain receptors in dogs with portal-systemic encephalopathy. Life Sci. 1991 ; 48:37-50.

48. Macdonald GA, Frey KA, Agranoff BW, Minoshima S, Koeppe RA, Kuhl DE, Shulkin BL, Lucey MR. Cerebral benzodiazepine receptor binding in vivo in patients with recurrent hepatic encephalopathy. Hepatology. 1997; 26:277-82.

49. Avallone R, corsi L, Zeneroli ML, Baraldi M: Presence of benzodiazepine-like molecules in food and their implication in the nutrition of cirrhotic patients. *Inn Food Sc. Technol* 2001:23 ; 193-198

50. Basile AS, Harrison PM, Hughes RD, Gu ZQ, Pannelle L, Mckinsety, A, Jones EA, Williams R. Relationship between plasma benzodiazepine receptor ligand concentrations and severity of hepatic encephalopathy. *Hepatology* 1994:11:112-121

51. Nielsen K, Kondrup J, Martinsen L, Døssing H, Larsson B, Stilling B, et al. Longterm oral refeeding of patients with cirrhosis of the liver. *Br J Nutr* 1995;74:55767.

52. Córdoba J, López-Hellín J, Planas M, Sabín P, Sanpedro F, Castro F: Normal diet for episodic hepatic encephalopathy: results of a randomized study. *J Hepatol* 2004; 41: 38–43.

53. Kearns PJ, Young H, Garcia G, Blaschke T, O'Hanlon G, Rinki M, et al. Accelerated improvement of alcoholic liver disease with enteral nutrition. *Gastroenterology* 1992; 102:2005.

54. Morgan TR, Moritz TE, Mendenhall CL, Haas R, and VA Cooperative Study Group #275. Protein consumption and hepatic encephalopathy in alcoholic hepatitis. *J Am Coll Nutr*1995 ; 14:1528.

55. Plauth M, Merli M, Kondrup J,Weimann A, Ferenci P, Müller MJ, ESPEN Consensus Group. ESPEN guidelines for nutrition in liver disease and transplantation. *Clin Nutr* 1997 ; 16:4355.

56. Als-Nielsen B, Gluud LL, Gluud C. Non-absorbable disaccharides for hepatic encephalopathy: systematic review of randomised trials. *BMJ* 2004; 328:1046-1050.

57. Rolachon A, Zarski JP, Lutz JM, Fournet J, Hostein J. [Is the intestinal lavage with a solution of mannitol effective in the prevention of post-hemorrhagic hepatic encephalopathy in patients with liver cirrhosis? Results of a randomized prospective study] *Gastroenterol Clin Biol.* 1994 ; 18:1057-62. French.

58. Festi D, Vestito A, Mazzella G, Roda E, Colecchia A. Management of hepatic encephalopathy: Focus on Antibiotic Therapy. *Digestion* 2006;73(suppl 1):94–101.

59. Fast BB, Wolfe SJ, Stormont JM, Davidson CS. Antibiotic therapy in the management of hepatic coma. *Arch Intern Med* 1958 ; 101:467-75.

60. Solga S F, Diehl A M. Gut flora-based therapy in liver disease? The liver cares about the gut. *Hepatology* 2004; 39:1197-1200.

61. Kircheis G, Nilius R, Held C, Berndt H, Buchner M, Gortelmeyer R, et al. Therapeutic efficacy of L-ornithine-L-aspartate infusions in patients with cirrhosis and hepatic encephalopathy: results of a placebo-controlled, double-blind study. *Hepatology* 1997;25:1351-1360.

62. Riggio O, Merli M, Capocaccia L, Caschera M, Zullo A, Pinto G, et al. Zinc Supplementation reduces blood ammonia and increases liver rnithine transcarbamylase activity in experimental cirrhosis. *Hepatology* 1992; 16:785-9.

63. Sushma S, Dasarathy S, Tandon RK, Jain S, Gupta S, Bhist MS. Sodium benzoate in the treatment of acute hepatic encephalopathy: a double-blind randomized trial. *Hepatology* 1992;16:138-44.

64. Romero-Gomez M, Boza F, Garcia-Valdecasas MS, Garcia E, Aguilar-Reina J. Subclinical hepatic encephalopathy predicts the development of overt hepatic encephalopathy. Am J Gastroenterol 2001; 96:2718- 2723

65. Hartmann IJ, Groeneweg M, Quero JC, Beijeman SJ, de Man RA, Hop WC, Schalm SW. The prognostic significance of subclinical hepatic encephalopathy. Am J Gastroenterol. 2000; 95:2029-34.

66. Ortiz M, Jacas C, Cordoba J. Minimal hepatic encephalopathy: diagnosis, clinical significance and recommendations. J Hepatol 2005; 42 Suppl (1):S45-53.

67. Lockwood AH, Yap EW, Wong WH. Cerebral ammonia metabolism in patients with severe liver disease and minimal hepatic encephalopathy. J Cereb Blood Flow Metab 1991; 11:337- 341.

68. de Bruijn KM, Blendis LM, Zilm DH, Carlen PL, Anderson GH. Effect of dietary protein manipulation in subclinical portal-systemic encephalopathy. Gut 1983 ; 24:53-60.

69.

70. Gallai V, Alberti A, Balò S, Mazzotta G, Clerici C,Gentili G, Firenze C, Morelli A. Cognitive event-related potential in hepatic encephalopathy. Acta Neurol. Scand. 1995; 91:358–361.

71. Joebges E.M., Heidemann M., Schimke N., Hecker H., Ennen JC., Weissenborn,K. Bradykinesia in minimal hepatic encephalopathy is due to disturbances in movement initiation. J Hepatol. 2003; 38, 273-280.

72. Jones DP, Binnie CD, Bown RL, Lloyd DS, and Watson BW. The contingent negative variation and psychological findings in chronic hepatic encephalopathy. Electroencephalogr. Clin. Neurophysiol. 1976; 40:661– 665.

73. Kircheis G, Wettstein M, Timmermann L, Schnitzler A, Haussinger D. Critical flicker frequency for quantification of low-grade hepatic encephalopathy. Hepatology. 2002; 35:357-366.

Kramer L, Bauer E, Gendo A, Funk, G, Madl C, Pidlich, J, and Gangl A. Neurophysiological evidence of cognitive impairment in patients without hepatic encephalopathy after transjugular intrahepatic portosystemic shunts. Am. J. Gastroenterol. 2002, 97:162–166.

74. Kulisevsky J, Conill J, Avila A, Pujol J, Balanzo J, and Capdevila A. Abnormalities of the Bereitschaftspotential andMRI pallidal signal in non-encephalopathic cirrhotic patients. Electroencephalogr. Clin. Neurophysiol 1995; 94:425–431.

75. Kullmann, F., Hollerbach, S., Lock, G., Holstege, A., Dierks, T., and Sch¨olmerich, J. Brain electrical activity mapping of EEG for the diagnosis of (sub)clinical hepatic encephalopathy in chronic liver disease. Eur. J. Gastroenterol. Hepatol. 2001, 13:513–522.

76.

77. Montagnese S, Amodio P, and Morgan MY. Methods for diagnosing hepatic encephalopathy in patients with cirrhosis: A multidimensional approach. Metab. Brain Dis. 2004; 19:281–312.

78. Niedermeyer, E. Metabolic central nervous system disorders. In (E. Niedermeyer and F. Lopes Da Silva, eds.), Electroencephalography. Basic Principles, Clinical Applications, and Related Fields, Williams & Wilkins, Baltimore, pp. 416–431.

79. Parsons-Smith BG, Summerskill WHJ, Dawson AM, and Sherlock S. The electroencephalograph in liver disease. Lancet 1957; 2:867–871.

80. Quero JC, Hartmann IJ, Meulstee J, Hop WC, Schalm SW. The diagnosis of subclinical hepatic encephalopathy in patients with cirrhosis using neuropsychological tests and automated electroencephalogram analysis, Hepatology 1996, 24:556-60.

81. Reitan RM. The relation of the Trail Making Test to organic brain damage. J Consult Psychol 1955; 19: 393-4.

82. Schiff S, Vallesi A, Mapelli D, Orsato R, Pellegrini A, Umiltà C, Gatta A, Amodio P: Impairment of response inhibition precede motor alteration in the early stage of liver

cirrhosis. A behavioral and electrophysiologicalstudy. Met Brain Dis.2005,20115-127.

83. Wechsler D. (1981). Wechsler Adult Intelligence Scale – Revised, Psychological Corporation, New York.

84. Weissenborn K, Ennen JC, Schomerus H, Rückert N, Hecker H. Neuopsychological characterization of hepatic encephalopathy. J. Hepatol. 2001; 34:768–773.

A Study On Minimal Hepatic Encephalopathy

PROFORMA

S. No.

Name : Age: Sex:

Educational status:

Occupation:

Address:

Contact No.:

Hospital No.:

Symptoms:

i) Abdominal distension

ii) Swelling of legs

iii) Jaundice

iv) Blood vomiting

v) Abdominal pain

vi) Altered sleep rhythm / altered sensorium

vii) Bleeding tendencies

60
60
60

PAST HISTORY

i) Jaundice

ii) Abdominal surgeries

iii) Blood transfusion

iv) Tattooing

PERSONAL HISTORY

i) Alcohol

ii) Smoking

iii) Drug abuse

iv) Marital Status

v) Promiscuity

EXAMINATION

Consciousness : Orientation :

Pallor : Y/ N Jaundice : Y / N Pedal edema :

Lymphadenopathy : JVP :

Signs of CLD :

Cutaneous bleed :

Ascites :

Hepatosplenomegaly :

Abdominal wall collaterals :

Asterixis :

INVESTIGATIONS

1. Liver function tests

   T. Bilirubin :

   D. Bilirubin : T. Protein :

   Albumin :

   AST : Globulin :

   ALT :

2. Prothrombin Time / INR
3. Ultrasonography of the abdomen
4. Diagnostic Upper GI Endoscopy
5. Number Connection Test (NCT)
6. Electroencephalogram (EEG)
7. Brainstem auditory evoked potential (BAEP)

Master chart

Sl No
Name
Age.
Sex
Etiology of cirrhosis
NCT
EEG
BAEP
1
Mahendran
42
M
Alcohol
Abnormal
Normal
Abnormal prolongation of latency and asymmetry
2
Arunachalam
44
M
Alcohol
Normal
Abnormal suggestive of B/L cerebral dysfunction
Normal
3
Lalitha
38
F
Cryptogenic
Normal
Normal
Normal
4
Krishnan
44
M
Alcohol
Normal
Abnormal suggestive of B/L cerebral dysfunction
Abnormal prolongation of latency and asymmetry
5
Anandhi
37
F

Cryptogenic
Abnormal
Normal
Normal
6
Mahendri
45
F
HBV
Normal
Abnormal suggestive of B/L cerebral dysfunction
Normal
7
Saravanakumar
34
M
Cryptogenic
Abnormal
Normal
N
8
Venkateshwar
41
M
Alcohol
Normal
Normal
Abnormal prolongation of latency and asymmetry
9
Ponnamma
45
F
HBV
Normal
Normal
Normal
10
Kameshwari
52
F
Cryptogenic
Abnormal
Abnormal suggestive of B/L cerebral dysfunction
Normal
11
Sakuntala
52
F
HBV

Normal
Normal
Normal
12
Rajadurai
45
M
Alcohol
Abnormal
Normal
Abnormal prolongation of latency and asymmetry
13
Rajalakshmi
76
F
Cryptogenic
Normal
Abnormal suggestive of B/L cerebral dysfunction
Normal
14
Ramesh
36
M
Alcohol
Abnormal
Normal
Normal
15
Indrani
47
F
Cryptogenic
abnormal
Normal
Normal
16
Lakshmanan
58
M
Alcohol
Normal
Normal
Normal
17
Venkateshwari
39
F
Alcohol
Normal

Abnormal suggestive of B/L cerebral dysfunction
Abnormal prolongation of latency and asymmetry
18
Anbalagan
41
M
Cryptogenic
Normal
Normal
Normal

19
Lakshmanan
43
M
Cryptogenic
Abnormal
Normal
Normal
20
Dhanalakshmi
43
F
Alcohol
Abnormal
Normal
Normal
21
Malliga
35
F
Cryptogenic
Normal
Abnormal suggestive of B/L cerebral dysfunction
Normal
22
Mani
48
M
Alcohol
Abnormal
Normal
Abnormal prolongation of latency and asymmetry
23
Rajeshwari
38
F
Alcohol
Abnormal

Normal
Normal
24
Murugan
47
M
Cryptogenic
Abnormal
Abnormal suggestive of B/L cerebral dysfunction
Normal
25
Thiagarajan
38
M
Alcohol
Abnormal
Normal
Normal
26
Murugesan
54
M
HBV
Abnormal
Abnormal suggestive of B/L cerebral dysfunction
Abnormal prolongation of latency and asymmetry
27
Rajendran
45
M
Cryptogenic
Abnormal
Normal
Normal
28
Savithri
69
F
Cryptogenic
Normal
Normal
Normal
29
Kamaladevi
36
F
HBV
Abnormal
Abnormal suggestive of B/L cerebral dysfunction

Normal
30
Thangavel
60
M
Alcohol
Abnormal
Normal
Normal
31
Hari
50
M
Alcohol
Normal
Normal
Normal
32
Viswanathan
40
M
Alcohol
Abnormal
Normal
Abnormal prolongation of latency and asymmetry
33
Dhanapal
39
M
Alcohol
Normal
Normal
Normal
34
Ramasamy
47
M
HBV
Normal
Abnormal suggestive of B/L cerebral dysfunction
Normal
35
Madhu
43
M
Alcohol
Abnormal
Normal
Normal

36
Ramachandran
39
M
Cryptogenic
Normal
Normal
Normal
37
Adiappan
37
M
Alcohol
Normal
Normal
Abnormal prolongation of latency and asymmetry
38
Kanniappan
60
M
Alcohol
Abnormal
Normal
Normal
39
Balaraman
45
M
Alcohol
Abnormal
Abnormal suggestive of B/L cerebral dysfunction
Normal
40
Balan
42
M
Cryptogenic
Normal
Normal
Normal

41
Ramayee
61
F
Alcohol
Abnormal
Abnormal suggestive of B/L cerebral dysfunction
Abnormal prolongation of latency and asymmetry

42
Chinnathambi
54
M
Alcohol
Abnormal
Normal
Normal
43
Simon
43
M
HBV
Normal
Normal
Normal
44
Suseela
39
F
Alcohol
Normal
Normal
Normal
45
Nainan
56
M
Alcohol
Abnormal
Abnormal suggestive of B/L cerebral dysfunction
Abnormal prolongation of latency and asymmetry
46
Gopal
37
M
Alcohol
Normal
Normal
Normal
47
Palani
45
M
Alcohol
Normal
Normal
Normal
48

Venkatesan
41
M
Alcohol
Normal
Normal
Normal
49
Mahalingam
38
M
Alcohol
Normal
Normal
Normal
50
venugopal
52
M
Alcohol
Normal
Abnormal suggestive of B/L cerebral dysfunction
Abnormal prolongation of latency and asymmetry

PATIENT CONSENT FORM

STUDY TITLE : A Study On Minimal Hepatic Encephalopathy

Study Centre **:** Department of Medical Gastroenterology, MMC, GGH, Chennai – 600003.

Patient's Name **:**

Patient's Age **:**

Identification Number **:**

Patients may check (□) these Boxes

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask the questions and all my questions and doubts have been answered to my complete satisfaction.	[ ]
I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving any reason, without my legal right being affected	[ ]
I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethics committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from study. I agree to this access, however, I understand that my identity would not be revealed. In any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study.	[ ]
I agree to take part in the above study and to comply with the instructions given during the study and to faithfully to cooperate with the study team, and to immediately inform the study staff if I suffer from any deterioration in my health or my well being or any unexpected or unusual symptoms.	[ ]
I hereby give consent to participate in this study .	[ ]

Signature/ Thumb Impression of the patient:	....
Place :	.....
Patient's name and address:	....
Signature of the Investigator	.....Place ..... Date .....

Name of the Investigator	.....